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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF: :

KEN HASSEN : EXAMINER: TRAN

SERIAL NO. : 10/073,978 :

FILED: FEBRUARY 14, 2002 : GROUP ART UNIT: 1615

FOR: ULTRAFINE L-CARNITINE, METHODS OF PREPARING THE SAME, COMPOSITIONS CONTAINING THE SAME, AND METHODS OF USING THE SAME

# APPEAL BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VA 22313-1450

SIR:

This is an appeal of the Final Rejection of Claims 11-14 in the above-identified application set forth in the Official Action mailed November 29, 2002 and maintained in the Advisory Action mailed April 15, 2003.

## I. Real Party of Interest

The real party of interest in this appeal is Sigma-Tau HealthScience, S.p.A. having an address of Via Treviso 4, Pomezia RM, Italy 00040.

## II. Related Appeals and Interferences

Appellants, Appellants' legal representative and their assignee are not aware of any appeals or interferences which will directly affect or be directly affected by or having a bearing on the Board's decision in this appeal.

III. Status of Claims

Claims 1-14 are the only claims pending in the above-identified application.

Claims 1-14 are appealed herein.

IV. Status of Amendments filed under 37 C.F.R. §1.116

The Amendment Under 37 C.F.R. §1.116, along with the executed Declaration under 37 C.F.R. §1.132, filed March 31, 2003 have been entered and considered not to be persuasive to the allowance of the claims over the prior art under 35 U.S.C. §103(a).

V. Summary of Invention

L-carnitine is known to have many uses, including oral administration as an effective therapeutic for cardiovascular diseases (page 2, lines 2-3). L-carnitine and its salts are also useful as a dietary supplement, in particular for the facilitation of the metabolism of lipids (page 2, lines 3-5). However, problems existing in the art with conventional forms of L-carnitine have given rise to a need to: (a) increase the bioavailability of L-carnitine and its well known salts, (b) prepare compositions which contain L-carnitine and one or more other ingredients with which bulk L-carnitine is not miscible, e.g., oil-based raw materials, and (c) reduce the hygroscopicity of L-carnitine (page 2, lines 6-10).

Consequently, in the present invention, Appellants have provided a novel form of L-carnitine and salts thereof, which address the aforementioned problems that exist with conventional forms of L-carnitine (page 8, line 4 to page 9, line 4). Present Claims 1-3 relate L-carnitine having a particle size such that it substantially passes through a 100 USBS mesh sieve (referred to as "ultrafine L-carnitine"). Present Claims 4-6 relate to methods for preparing such ultrafine L-carnitine. Present Claims 7-11 relate to compositions that contain

such ultrafine L-carnitine. Present Claims 12-14 relate to methods of treatment using such ultrafine L-carnitine.

VI. Issues

Whether Claims 1-14 are obvious within the meaning of 35 U.S.C. §103(a) over U.S. Patent No. 4,602,039 (Cavazza I) in view of U.S. Patent No. 6,063,820 (Cavazza II).

VII. Grouping of the Claims

For this issue on appeal, the claims stand or fall together.

VIII. Arguments

Claims 1-14 stand rejected under 35 U.S.C. §103(a) as unpatentable over U.S. Patent No. 4,602,039 (Cavazza I) in view of U.S. Patent No. 6,063,820 (Cavazza II). This rejection is untenable and should not be sustained.

Present Claims 1-3 relate L-carnitine having a particle size such that it substantially passes through a 100 USBS mesh sieve (hereinafter referred to as "ultrafine L-carnitine"). Present Claims 4-6 relate to methods for preparing such ultrafine L-carnitine. Present Claims 7-11 relate to compositions that contain such ultrafine L-carnitine. Present Claims 12-14 relate to methods of treatment using such ultrafine L-carnitine.

The Appellant has discovered that the presently claimed ultrafine L-carnitine provides a number of advantages as compared to conventional L-carnitine. The cited references provide no teaching which would suggest the presently claimed ultrafine L-carnitine, or the various claimed compositions and methods. Accordingly, these references cannot affect the patentability of the present claims.

Cavazza I (U.S. Patent No. 4,602,039) is discussed on page 5, lines 14-22, of the specification. Thus, as explained in the specification, the undisputed difference between the L-carnitine of Cavazza I and the presently claimed ultrafine L-carnitine is that the presently claimed ultrafine L-carnitine and salts thereof have a particle sufficiently small that substantially all of it passes through a 100, or even a 150 or 200, United States Bureau of Standards (USBS) mesh screen. In contrast, the L-carnitine and salts thereof prepared by the methods described in Cavazza I have a particle size such that more than 10% by weight of the L-carnitine is retained by a 50 mesh sieve and more than 40% by weight is retained by a 100 mesh sieve. Furthermore, not only is this deficiency in the Cavazza references undisputed, the Examiner has explicitly recognized this deficiency stating: "The Examiner notes that that cited references do not teach the claimed particle sieve size" (paper number 5, page 3, lines 7-8).

The Examiner dismisses this clear and conceded difference instead stating that Appellants have not limited the claims such that a percent by weight of L-carnitine passes through a 100 USBS mesh sieve. In so doing the Examiner has taken the position that any L-carnitine that passes through a 100 USBS mesh sieve would necessarily be the same as that claimed. Appellants disagree with this over-generalized assertion. Moreover, Appellants wish to remind the Examiner that: "Applicants are their own lexicographer" (MPEP §2173.01 citing *In re Swinehart*, 439 F.2d 210, 160 USPQ 226 (CCPA 1971)). MPEP §2173.01 also states that Applicants "can define in the claims what they regard as their invention essentially in whatever terms they choose so long as the terms are not used in ways that are contrary to accepted meanings in the art." Further, MPEP §2173.02 provides guidance as to analysis of the definiteness of claim language mandating that definiteness must not be analyzed in a vacuum, but in light of:

(A) The content of the particular application disclosure;

(B) The teachings of the prior art; and

(C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made (MPEP §2173.02).

Appellants note that the specification at page 5, lines 6-13, recites:

> The ultra-fine L-carnitine and salts thereof of the present invention has a particle sufficiently small that substantially all of it passes through a 100 United State Bureau of Standards (USBS) mesh screen. In a preferred embodiment, the ultra-fine L-carnitine and salts thereof of the present invention has a particle sufficiently small that substantially all of it passes through a 150 USBS mesh screen. In a particularly preferred embodiment, the ultra-fine L-carnitine and salts thereof of the present invention has a particle sufficiently small that substantially all of it passes through a 200 USBS mesh screen.

Further, page 6, lines 9-12 of the specification recites:

> The ultra-fine L-carnitine of the present invention is obtained by selecting that material which passes through a 100 USBS mesh sieve, preferably a 150 USBS mesh sieve, more preferably a 200 mesh USBS mesh sieve.

Accordingly, Appellants submit that based on the specification, the skilled artisan would readily appreciated that the term "substantially" set forth in the claim does not include any and all L-carnitine particles and/or mixtures that pass through a 100 USBS mesh sieve, but rather the ultra-fine L-carnitine of the present claims specifically refer to a situation where substantially all (nearly 100%) of the particles pass through a 100 USBS mesh sieve. The fact that the Examiner recognizes that about 40% by weight of carnitine in Cavazza I is retained by a mesh sieve (paper number 10, page 2, line 22 to page 3, line 1) further underscores that fact that the Examiner does not dispute that Cavazza I is *distinct* from the claimed invention.

Despite the numerous and distinct advantages proffered by the presently claimed ultrafine L-carnitine, which Appellant submits could not have been expected based on the teachings of the cited references (see Amendment and Request for Reconsideration filed on November 4, 2002, as well as pages 1-5 of the present specification), the Examiner chooses to

dismiss these advantages and question the criticality of the claimed specific particle sieve size. To address the Examiner's assertions and questions, Appellant encloses herewith a copy of the executed Declaration under 37 C.F.R. §1.132 by Mr. Raj K. Chopra filed on March 31, 2003 (hereinafter referred to as the "Chopra Declaration").

As demonstrated in the Chopra Declaration and the attached *curriculum vitae*, Mr. Raj K. Chopra is currently the President and Chief Scientific Officer of Tishcon Corporation (Westbury, NY) and has 34 years of experience in the Nutritional Supplement Industry. In addition to numerous scientific presentations and publications, Mr. Chopra has accumulated an expertise in the areas of: a) formulation of solid, semisolid and liquid dosage forms; b) taste and flavor masking of micro and macronutrients; c) enhancing dissolution and bioavailability of nutrients; and d) formulating test supplements for clinical trials. Equally importantly, Mr. Chopra is a significant user of ultrafine L-carnitine and is very familiar with its properties and uses.

After reviewing Cavazza I, Cavazza II (U.S. Patent No. 6,063,820), the specification and claims of the above-identified application, and the June 4, 2002 Office Action, Mr. Chopra has provided the attached Chopra Declaration highlighting the fact that "the ultrafine L-carnitine described and claimed in the present application exhibits a number of unexpected advantages as compared to the L-carnitine described in Cavazza" (see numbered paragraph 9). Appellant notes that the claims have not been amended in response to the June 4, 2002 Office Action and the obviousness rejection over Cavazza I in view of Cavazza II has been maintained and reissued in the November 29, 2002 Office Action. Accordingly, the Chopra Declaration is appropriate and applicable to address the current rejection explicated in the November 29, 2002 Office Action.

As stated in the Chopra Declaration, Mr. Chopra's opinion is based on experience and use of both the ultrafine L-carnitine described and claimed in the present application and the

conventional L-carnitine described in Cavazza (see paragraph 11 of the Chopra Declaration). Specifically, Mr. Chopra has used both conventional L-carnitine and ultrafine L-carnitine provided by Sigma-Tau Healthsciences in the formulation of dietary supplement dosage forms (soft gelatin capsules, hard gelatin capsules, and tablets) at Tishcon Corporation and have found that the ultrafine L-carnitine provides the following unexpectedly superior results:

A. The particle size reduction achieved with the claimed ultrafine L-carnitine has enabled Tishcon Corporation to design a soft-gel dosage form of ultrafine L-carnitine (for example fumarate) in combination with 1) omega-3 fatty acids in fish oil; 2) coenzyme Q10; and 3) alpha lipoic acid. The same good results have not been obtained using L-carnitine produced according to Cavazza I (see paragraph 12 of the Chopra Declaration).

B. The fineness of the particle size, as well as the particle size range of the claimed ultrafine L-carnitine, provides an ideal physical form to ensure content uniformity when filling multi-component active products in two piece hard gelatin capsules. Furthermore, Tishcon Corporation has been able to obtain a high degree of color uniformity in its tablets made with the claimed ultrafine L-carnitine. Particularly, in the soft gelatin encapsulation process, where the L-carnitine (for example fumarate) is processed into a paste with added vegetable oils, the particle size is a critical factor. The claimed ultrafine L-carnitine performs perfectly in this process, while the conventional L-carnitine (for example fumarate) with its larger particle size range causes severe filling as well as sealing problems (see paragraph 13 of the Chopra Declaration).

C. Due to the extremely fine state of subdivision afforded by the presently claimed ultrafine L-carnative, Tishcon Corporation is able to pack the powder more firmly in capsules, thereby leaving very little interstitial spaces between

particles. This is probably the reason why these capsules do not exhibit premature:

- discoloration;
- development of unacceptable odor;
- moisture pick-up; and
- physico-chemical instability (see paragraph 14 of the Chopra Declaration).

Mr. Chopra also states that the ultra-fine L-carnitine and salts thereof of the present invention has a particle sufficiently small that substantially all of it passes through a 100, 150, or 200 United State [*sic*, States] Bureau of Standards (USBS) mesh screen, while L-carnitine and salts thereof prepared by the methods described in Cavazza I have size of such that greater than 10% by weight of the L-carnitine is retained by a 50 mesh sieve and more than 40% by weight is retained by a 100 mesh sieve (see paragraph 11 of the Chopra Declaration). Moreover, Mr. Chopra states that these results would not be expected based on the disclosure of Cavazza I (see paragraph 11 of the Chopra Declaration).

Thus, at the time the present invention was made there was a need for preparing compositions containing L-carnitine and one or more other ingredients with which bulk L-carnitine is not miscible, (*e.g.*, oil-based raw materials). Moreover, at the time the present invention was made there was also a need for reducing the hygroscopicity of L-carnitine.

In other words, even though the L-carnitine (for example the fumarate salt) prepared according to Cavazza I demonstrates an improvement in handling abilities, for example for tabletting, over previous forms of carnitine, the L-carnitine prepared according to Cavazza I still possesses a particle size and bulk density that is less than ideal for certain other applications, such as containment within hard and soft geltain capsules (see paragraph 10 of

the Chopra Declaration). For this reason, many transformers rejected its use for hard and soft gel applications, choosing to remain with tablets.

It was not obvious to reduce the size of the particles as disclosed in the present application, since this was felt unworkable (see paragraph 10 of the Chopra Declaration). Specifically, carnitine in any form is seldom a candidate for particle size reduction, because the frictional heat generated during the particle size reduction process may induce the humid state relative to the ambient air temperature and thereby produce sticking (see paragraph 10 of the Chopra Declaration).

For the reasons set forth above and in the Chopra Declaration, the presently claimed ultrafine L-carnitine is not obvious in light of Cavazza I and the claimed particle sieve size is, in fact, a critical parameter, which provides *unexpectedly superior* results.

In the Advisory Action, the Examiner chooses to dismiss the Chopra Declaration for the following reasons: (1) It is Chopra's opinion, (2) the use of a capsule is not required in the claims, (3) Cavazza I does teach that L-carnitine can be used to prepare orally administrable dosage form, including, tablet and capsule, and (4) there is no data showing the capsule taught by Cavazza I would exhibit premature discoloration, development of unacceptable odor, moisture pick-up, and physico-chemical instability (paper number 10, page 4, lines 10-16).

With respect to points (2) and (3), Appellants note that the usage of a capsule and the administerability by oral dosage forms are merely exemplary of the advantageous results obtainable from the invention. The Examiner appears to focus on these points as limitations; however, this focus clearly overlooks the critical difference between the present invention and the disclosure of Cavazza I, the particle size of the L-carnitine.

Regarding points (1) and (4) of the Examiner's reasons for disregarding the clear showing by the Chopra Declaration of the differences of between the present invention and Cavazza I, Appellants note that the Declaration has been provided by an expert in the field

who is declaring that which would be apparent to the skilled artisan based on the disclosures of Cavazza I and Cavazza II. By its very definition, such a declaration is the "*opinion* of one skilled in the art."

Appellants note that rebuttal evidence may include evidence of the state of the art, the level of skill in the art, and the beliefs of those skilled in the art. See, e.g., *In re Oelrich,* 579 F.2d 86, 91-92, 198 USPQ 210, 214 (CCPA 1978) (Expert opinions regarding the level of skill in the art were probative of the nonobviousness of the claimed invention.).

Appellant submits that Cavazza II cannot cure the basic deficiencies of Cavazza I for the following reasons. In the Advisory Action, the Examiner states that "Cavazza II only using ultrafine L-carnitine in combination with..." (see paper number 10, page 3, lines 7). However, the L-carnitine used in Cavazza II is produced using the method described in Cavazza I and, thus, has the characteristics of that of Cavazza I. In other words, Cavazza II discloses carnitine and salts thereof in combination with other active ingredients, and at no point does Cavazza II disclose or suggest the claimed ultrafine L-carnitine.

Moreover, as explained above, only by using ultrafine L-carnitine in combination with omega-3 fatty acids in fish oil or coenzyme Q10, or alpha lipoic acid, is it possible to obtain an easily workable mixture. The same good results would not have been obtained using L-carnitine produced according to Cavazza I.

Again, Cavazza II does not mention or suggest the use of the ultrafine L-carnitine according to the present claims. Therefore, for these reasons Cavazza II alone, or even in combination with Cavazza I, can not render the present invention obvious.

Based on the foregoing, supported by the Chopra Declaration, Applicants submit that the presently claimed ultrafine L-carnitine is not obvious in view of the combined disclosures of Cavazza I and Cavazza II. In particular, the claimed particle sieve size is, in fact, a critical parameter, which provides *unexpectedly superior* results.

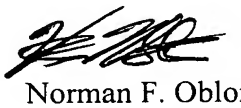
Accordingly, it is respectfully requested that this rejection be REVERSED.

## IX. CONCLUSION

For the above reasons, Claims 1-14 are not unpatentable under 35 U.S.C. §103 (a) over U.S. Patent No. 4,602,039 (Cavazza I) in view of U.S. Patent No. 6,063,820 (Cavazza II). Therefore, the Examiner's rejections should be REVERSED.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



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Attachments: Appendix
Executed Declaration under 37 C.F.R. §1.132 by Mr. Raj K. Chopra filed on March 31, 2003

## Appendix

Pending Claims in U.S. Application Serial No. 10/073,978

1. L-carnitine, having a particle size such that it substantially passes through a 100 USBS mesh sieve.

2. The L-carnitine of Claim 1, which is selected from the group consisting of L-carnitine, salts of L-carnitine, alkanoyl L-carnitines, and salts of alkanoyl L-carnitine.

3. The L-carnitine of Claim 1, which is selected from the group consisting of L-carnitine chloride, L-carnitine bromide, L-carnitine orotate, L-carnitine acid aspartate, L-carnitine acid phosphate, L-carnitine fumarate, L-carnitine lactate, L-carnitine maleate, L-carnitine acid maleate, L-carnitine acid oxalate, L-carnitine acid sulfate, L-carnitine glucose phosphate, L-carnitine tartrate, L-carnitine acid tartrate, L-carnitine iodate, L-carnitine aspartate, L-carnitine citrate, L-carnitine acid citrate, L-carnitine acid fumarate, L-carnitine glycerophosphate, L-carnitine mucate, L-carnitine orotate, L-carnitine oxalate, L-carnitine sulfate, L-carnitine trichloroacetate, L-carnitine trifluoroacetate, L-carnitine methanesulfonate, L-carnitine pamoate, L-carnitine acid pamoate, $C_{2-8}$ alkanoyl L-carnitines, $C_{2-8}$ alkanoyl L-carnitine chloride, $C_{2-8}$ alkanoyl L-carnitine bromide, $C_{2-8}$ alkanoyl L-carnitine orotate, $C_{2-8}$ alkanoyl L-carnitine acid aspartate, $C_{2-8}$ alkanoyl L-carnitine acid phosphate, $C_{2-8}$ alkanoyl L-carnitine fumarate, $C_{2-8}$ alkanoyl L-carnitine lactate, $C_{2-8}$ alkanoyl L-carnitine maleate, $C_{2-8}$ alkanoyl L-carnitine acid maleate, $C_{2-8}$ alkanoyl L-carnitine acid oxalate, $C_{2-8}$ alkanoyl L-carnitine acid sulfate, $C_{2-8}$ alkanoyl L-carnitine glucose phosphate, $C_{2-8}$ alkanoyl L-carnitine tartrate, $C_{2-8}$ alkanoyl L-carnitine acid tartrate, $C_{2-8}$ alkanoyl L-carnitine iodate, $C_{2-8}$ alkanoyl L-carnitine aspartate, $C_{2-8}$ alkanoyl L-carnitine citrate, $C_{2-8}$ alkanoyl L-carnitine acid citrate, $C_{2-8}$ alkanoyl L-carnitine acid fumarate, $C_{2-8}$ alkanoyl L-carnitine glycerophosphate, $C_{2-8}$ alkanoyl L-carnitine mucate, $C_{2-8}$ alkanoyl L-carnitine orotate, $C_{2-8}$ alkanoyl L-carnitine oxalate, $C_{2-8}$ alkanoyl L-carnitine sulfate, $C_{2-8}$ alkanoyl L-

carnitine trichloroacetate, $C_{2-8}$ alkanoyl L-carnitine trifluoroacetate, $C_{2-8}$ alkanoyl L-carnitine methanesulfonate, $C_{2-8}$ alkanoyl L-carnitine pamoate, and $C_{2-8}$ alkanoyl L-carnitine acid pamoate.

4. A method of preparing L-carnitine, having a particle size such that it substantially passes through a 100 USBS mesh sieve, comprising:

(1) subjecting L-carnitine having a particle size such that it does not pass through a 100 USBS mesh sieve to size reduction, to obtain size-reduced L-carnitine; and

(2) subjecting said size-reduced L-carnitine to sieving through a 100 USBS mesh sieve and selecting that portion which passes through said 100 USBS mesh sieve.

5. The method of Claim 4, wherein said L-carnitine is selected from the group consisting of L-carnitine, salts of L-carnitine, alkanoyl L-carnitines, and salts of alkanoyl L-carnitine.

6. The method of Claim 4, wherein said L-carnitine is selected from the group consisting of L-carnitine chloride, L-carnitine bromide, L-carnitine orotate, L-carnitine acid aspartate, L-carnitine acid phosphate, L-carnitine fumarate, L-carnitine lactate, L-carnitine maleate, L-carnitine acid maleate, L-carnitine acid oxalate, L-carnitine acid sulfate, L-carnitine glucose phosphate, L-carnitine tartrate, L-carnitine acid tartrate, L-carnitine iodate, L-carnitine aspartate, L-carnitine citrate, L-carnitine acid citrate, L-carnitine acid fumarate, L-carnitine glycerophosphate, L-carnitine mucate, L-carnitine orotate, L-carnitine oxalate, L-carnitine sulfate, L-carnitine trichloroacetate, L-carnitine trifluoroacetate, L-carnitine methanesulfonate, L-carnitine pamoate, L-carnitine acid pamoate, $C_{2-8}$ alkanoyl L-carnitines, $C_{2-8}$ alkanoyl L-carnitine chloride, $C_{2-8}$ alkanoyl L-carnitine bromide, $C_{2-8}$ alkanoyl L-carnitine orotate, $C_{2-8}$ alkanoyl L-carnitine acid aspartate, $C_{2-8}$ alkanoyl L-carnitine acid phosphate, $C_{2-8}$ alkanoyl L-carnitine fumarate, $C_{2-8}$ alkanoyl L-carnitine lactate, $C_{2-8}$ alkanoyl L-carnitine maleate, $C_{2-8}$ alkanoyl L-carnitine acid maleate, $C_{2-8}$ alkanoyl L-carnitine acid

oxalate, $C_{2-8}$ alkanoyl L-carnitine acid sulfate, $C_{2-8}$ alkanoyl L-carnitine glucose phosphate, $C_{2-8}$ alkanoyl L-carnitine tartrate, $C_{2-8}$ alkanoyl L-carnitine acid tartrate, $C_{2-8}$ alkanoyl L-carnitine iodate, $C_{2-8}$ alkanoyl L-carnitine aspartate, $C_{2-8}$ alkanoyl L-carnitine citrate, $C_{2-8}$ alkanoyl L-carnitine acid citrate, $C_{2-8}$ alkanoyl L-carnitine acid fumarate, $C_{2-8}$ alkanoyl L-carnitine glycerophosphate, $C_{2-8}$ alkanoyl L-carnitine mucate, $C_{2-8}$ alkanoyl L-carnitine orotate, $C_{2-8}$ alkanoyl L-carnitine oxalate, $C_{2-8}$ alkanoyl L-carnitine sulfate, $C_{2-8}$ alkanoyl L-carnitine trichloroacetate, $C_{2-8}$ alkanoyl L-carnitine trifluoroacetate, $C_{2-8}$ alkanoyl L-carnitine methanesulfonate, $C_{2-8}$ alkanoyl L-carnitine pamoate, and $C_{2-8}$ alkanoyl L-carnitine acid pamoate.

7. A composition, comprising:

(A) L-carnitine having a particle size such that it substantially passes through a 100 USBS mesh sieve; and

(B) a pharmaceutically acceptable excipient or carrier.

8. The composition of Claim 7, wherein said L-carnitine is selected from the group consisting of L-carnitine, salts of L-carnitine, alkanoyl L-carnitines, and salts of alkanoyl L-carnitine.

9. The composition of Claim 7, wherein said L-carnitine is selected from the group consisting of L-carnitine chloride, L-carnitine bromide, L-carnitine orotate, L-carnitine acid aspartate, L-carnitine acid phosphate, L-carnitine fumarate, L-carnitine lactate, L-carnitine maleate, L-carnitine acid maleate, L-carnitine acid oxalate, L-carnitine acid sulfate, L-carnitine glucose phosphate, L-carnitine tartrate, L-carnitine acid tartrate, L-carnitine iodate, L-carnitine aspartate, L-carnitine citrate, L-carnitine acid citrate, L-carnitine acid fumarate, L-carnitine glycerophosphate, L-carnitine mucate, L-carnitine orotate, L-carnitine oxalate, L-carnitine sulfate, L-carnitine trichloroacetate, L-carnitine trifluoroacetate, L-carnitine methanesulfonate, L-carnitine pamoate, L-carnitine acid pamoate, $C_{2-8}$ alkanoyl L-carnitines,

$C_{2-8}$ alkanoyl L-carnitine chloride, $C_{2-8}$ alkanoyl L-carnitine bromide, $C_{2-8}$ alkanoyl L-carnitine orotate, $C_{2-8}$ alkanoyl L-carnitine acid aspartate, $C_{2-8}$ alkanoyl L-carnitine acid phosphate, $C_{2-8}$ alkanoyl L-carnitine fumarate, $C_{2-8}$ alkanoyl L-carnitine lactate, $C_{2-8}$ alkanoyl L-carnitine maleate, $C_{2-8}$ alkanoyl L-carnitine acid maleate, $C_{2-8}$ alkanoyl L-carnitine acid oxalate, $C_{2-8}$ alkanoyl L-carnitine acid sulfate, $C_{2-8}$ alkanoyl L-carnitine glucose phosphate, $C_{2-8}$ alkanoyl L-carnitine tartrate, $C_{2-8}$ alkanoyl L-carnitine acid tartrate, $C_{2-8}$ alkanoyl L-carnitine iodate, $C_{2-8}$ alkanoyl L-carnitine aspartate, $C_{2-8}$ alkanoyl L-carnitine citrate, $C_{2-8}$ alkanoyl L-carnitine acid citrate, $C_{2-8}$ alkanoyl L-carnitine acid fumarate, $C_{2-8}$ alkanoyl L-carnitine glycerophosphate, $C_{2-8}$ alkanoyl L-carnitine mucate, $C_{2-8}$ alkanoyl L-carnitine orotate, $C_{2-8}$ alkanoyl L-carnitine oxalate, $C_{2-8}$ alkanoyl L-carnitine sulfate, $C_{2-8}$ alkanoyl L-carnitine trichloroacetate, $C_{2-8}$ alkanoyl L-carnitine trifluoroacetate, $C_{2-8}$ alkanoyl L-carnitine methanesulfonate, $C_{2-8}$ alkanoyl L-carnitine pamoate, and $C_{2-8}$ alkanoyl L-carnitine acid pamoate.

10. The composition of Claim 7, which is suitable for oral ingestion.

11. The composition of Claim 7, which further comprises hydroxycitric acid, Co-enzyme Q10, chromium picolinate, gamma linolenic acid, resveratrol, omega 3 acids, an antioxidant, or a vitamin.

12. In a method of treatment, therapy, or prevention, comprising orally administering an effective amount of L-carnitine to a subject in need thereof, the improvement being said L-carnitine has a particle size such that it substantially passes through a 100 USBS mesh sieve.

13. The method of Claim 12, wherein said L-carnitine is selected from the group consisting of L-carnitine, salts of L-carnitine, alkanoyl L-carnitines, and salts of alkanoyl L-carnitine.

14. The method of Claim 12, wherein said L-carnitine is selected from the group consisting of L-carnitine chloride, L-carnitine bromide, L-carnitine orotate, L-carnitine acid

aspartate, L-carnitine acid phosphate, L-carnitine fumarate, L-carnitine lactate, L-carnitine maleate, L-carnitine acid maleate, L-carnitine acid oxalate, L-carnitine acid sulfate, L-carnitine glucose phosphate, L-carnitine tartrate, L-carnitine acid tartrate, L-carnitine iodate, L-carnitine aspartate, L-carnitine citrate, L-carnitine acid citrate, L-carnitine acid fumarate, L-carnitine glycerophosphate, L-carnitine mucate, L-carnitine orotate, L-carnitine oxalate, L-carnitine sulfate, L-carnitine trichloroacetate, L-carnitine trifluoroacetate, L-carnitine methanesulfonate, L-carnitine pamoate, L-carnitine acid pamoate, $C_{2-8}$ alkanoyl L-carnitines, $C_{2-8}$ alkanoyl L-carnitine chloride, $C_{2-8}$ alkanoyl L-carnitine bromide, $C_{2-8}$ alkanoyl L-carnitine orotate, $C_{2-8}$ alkanoyl L-carnitine acid aspartate, $C_{2-8}$ alkanoyl L-carnitine acid phosphate, $C_{2-8}$ alkanoyl L-carnitine fumarate, $C_{2-8}$ alkanoyl L-carnitine lactate, $C_{2-8}$ alkanoyl L-carnitine maleate, $C_{2-8}$ alkanoyl L-carnitine acid maleate, $C_{2-8}$ alkanoyl L-carnitine acid oxalate, $C_{2-8}$ alkanoyl L-carnitine acid sulfate, $C_{2-8}$ alkanoyl L-carnitine glucose phosphate, $C_{2-8}$ alkanoyl L-carnitine tartrate, $C_{2-8}$ alkanoyl L-carnitine acid tartrate, $C_{2-8}$ alkanoyl L-carnitine iodate, $C_{2-8}$ alkanoyl L-carnitine aspartate, $C_{2-8}$ alkanoyl L-carnitine citrate, $C_{2-8}$ alkanoyl L-carnitine acid citrate, $C_{2-8}$ alkanoyl L-carnitine acid fumarate, $C_{2-8}$ alkanoyl L-carnitine glycerophosphate, $C_{2-8}$ alkanoyl L-carnitine mucate, $C_{2-8}$ alkanoyl L-carnitine orotate, $C_{2-8}$ alkanoyl L-carnitine oxalate, $C_{2-8}$ alkanoyl L-carnitine sulfate, $C_{2-8}$ alkanoyl L-carnitine trichloroacetate, $C_{2-8}$ alkanoyl L-carnitine trifluoroacetate, $C_{2-8}$ alkanoyl L-carnitine methanesulfonate, $C_{2-8}$ alkanoyl L-carnitine pamoate, and $C_{2-8}$ alkanoyl L-carnitine acid pamoate.

Attorney Docket [redacted]219671US0CONT

**IN THE UNITED STATES PATENT & TRADEMARK OFFICE**

IN RE APPLICATION OF: :KEN HASSEN

: GROUP ART UNIT: 1615

SERIAL NO.: 10/073,978 : EXAMINER: TRAN, SUSAN T.

FILED: 02/14/2002

FOR: ULTRAFINE L-CARNITINE METHODS OF PREPARING THE SAME COMPOSITIONS CONTAINING THE SAME AND METHODS OF USING



**DECLARATION UNDER 37 C.F.R. §1.132**

ASSISTANT COMMISSIONER FOR PATENTS

WASHINGTON, D.C. 20231

SIR:

Now comes RAJ K. CHOPRA, who deposes and states that:

1. That I am a graduate of Gujarat University, India, and received my B.S. degree in Pharmacy (Honors) Gold Medalist, in the year 1965.

2. That I am also a graduate of Colombia University, and received my M.S. degree in Industrial Pharmaceutics in the year 1968.

3. That a copy of my curriculum vitae is attached hereto as Exhibit A and is incorporated into and is part of this declaration.

4. That I am currently the President and Chief Scientific Officer of Tishcon Corporation, Westburry, New York.

5. That I am a customer of Sigma-tau HealthScience Inc.

6. That I am using large quantities of ultrafine L-carnitine.

7. I do not receive compensation for my observations and comments within this declaration.

8. That I have reviewed the following:

   A. The specification and claims of U.S. Patent Application Serial No. 10/073,978 ("the '978 application");

   B. The Official Action dated June 4, 2002, in the 978 application;

and

C. U.S. Patent No. 4,602,039 (Cavazza)

D. U.S. Patent No. 6, 063,820 (Cavazza)

9. That is my opinion that the ultrafine L-carnitine described and claimed in the present application exhibits a number of unexpected advantages as compared to the L-carnitine described in Cavazza.

10. What was claimed in the '039 patent is a new non-hygroscopic salt of L-carnitine (for example L-carnitine fumarate). While L-carnitine fumarate in itself demonstrates an improvement in handling abilities over previous forms of carnitine for tabletting, it possesses a particle size and bulk density that is less than ideal for certain other applications, such as containment within hard and soft gelatin capsules. For this reason, many transformers rejected its use for hard and soft gel applications, choosing to remain with tablets. It was not obvious to reduce (micronize) the particles and use the specified flow agent, since this was felt unworkable, since carnitine in any form is not a candidate for particle reduction, since the frictional heat generated during the particle reduction process may induce the humid state relative to the ambient air temperature and thereby produce sticking. The trials by customers using regular L-carnitine fumarate vs. Ultrafine L-carnitine show that the finer, more free flowing characteristic of the latter finally allows blended content uniformity with other similarly particle sized ingredients, such as coenzyme Q10.

11. That my opinion is based on my experience and my use of both the ultrafine L-carnitine described and claimed in the present application and the conventional L-carnitine described in Cavazza. Specifically, I have used both conventional L-carnitine and ultrafine L-carnitine provided by Sigma-Tau Healthsciences in the formulation of dietary supplement dosage forms (soft gelatin capsules, hard gelatin capsules, and tablets) at Tishcon Corporation, and have found that ultrafine L-carnitine and salts thereof has a particle sufficiently small that substantially all of it passes through a 100 or 150, or 200 United State Bureau of Standards (USBS) mesh screen, while currently, L-carnitine and salts thereof prepared by the methods described in U.S. 4,602,039 yield L-carnitine having a size of such that greater than 10 % by weight of the L-carnitine is retained by a 50 mesh sieve and more than 40 % by weight is retained by a 100 mesh sieve; this characteristics renders ultrafine L-carnitine unexpectedly superior respect to the carnitine produced using the method described in U.S.

4,602,039.

12. The particle size reduction achieved with ultrafine L-carnitine has enabled Tishcon Corporation to design a soft-gel dosage form of ultrafine L-carnitine (for example fumarate) in combination with 1) omega-3 fatty acids in fish oil; 2) coenzyme Q10; and 3) alpha lipoic acid. The same good results have not been obtained using L-carnitine produced according to US 4,602,039.

13. The fineness of the particle size, as well as the particle size range of ultrafine L-carnitine, provides an ideal physical form to ensure content uniformity when filling multi-component active products in two piece hard gelatin capsules. Furthermore Tishcon Corporation has been able to obtain a high degree of color uniformity in its tables made with ultrafine L-carnitine. Particularly, in the soft gelatin encapsulation process, where the L-carnitine (for example fumarate) is processed into a paste with added vegetable oils, the particle size is a critical factor. Ultrafine L-carnitine performs perfectly in this process, while the conventional L-carnitine (for example fumarate) with its larger particle size range causes severe filling as well as sealing problems.

14. Due to the extremely fine state of subdivision afforded by ultrafine L-carnitine Tishcon Corporation is able to pack the powder more firmly in capsules, thereby leaving very little interstitial spaces between particles. This is probably the reason why these capsules do not exhibit premature:

1. Discoloration;
2. development of unacceptable odor;
3. moisture pick-up; and
4. physico-chemical instability

15. I declare further that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of this application or any patent issuing thereon.

DATE

March 7th, 2003

RAJK. CHOPRA

President

RAJ K. CHOPRA

Curriculum Vitae

Diploma, Pharmacy (Secured First position in the University, 1962)

B.S. Pharmacy (Honors) Gold Medalist, 1965 (Gujarat University, India)

M.S. (Industrial Pharmaceutics) Columbia University, 1968

Employment:

1977 - Present President and Chief Scientific Officer
Tishcon Corporation, Westbury, New York

1968 - 1977 Technical Director
PFI, Edison, New Jersey
(formerly Hempstead, New York)

1965 - 1968 Teaching Assistant, Columbia University
1967 Research Fellow (IFF), Columbia University
1966 Research Fellow (Sucrest Corp.), Columbia University

Experience:

34 years in the Nutritional Supplement Industry

Areas of Expertise:

- Formulation of solid, semisolid and liquid dosage forms.
- Taste and flavor masking of micro and macronutrients.
- Enhancing dissolution and bioavailability of nutrients.
- Formulating test supplements for clinical trials.

Publications:

"A new Coenzyme Q10 preparation with enhanced bioavailability."
R. Chopra, R. Goldman and H.N. Bhagavan
THE FASEB JOURNAL, Vol. II, No. 3, February 3, 1997.

"Evaluation of several materials as direct compression vehicles in pharmaceutical tableting." Thesis; 1968.

"Relative bioavailability of Coenzyme Q10 formulations in human

subjects."
R.K. Chopra, R. Goldman, S.T. Sinatra and H.N. Bhagavan
Int. J. Vitam. Nutr. Res., 1998; 68(2): 109-13

"Dietary Coenzyme Q10 and Vitamin E alter the status of these compounds
in rat tissues and mitochondria."
W.H. Ibrahim, H.N. Bhagavan, R.K. Chopra and C.K. Chow
J. Nutr, 2000 Sep; 130(9): 2343-2348

"Randomized, double-blind placebo-controlled trial of Coenzyme Q10 in patients with acute myocardial infarction."
R.B. Singh, G.S. Wander, A.Rastogi, P.K. Shukla, A. Mittal, J.P. Sharma

S.K. Mehrotra, Raj Kapoor and Raj K. Chopra
Cardiovascular Drugs and Therapy 1998; 12: 347-353

"Relative bioavailabilities of natural and synthetic Vitamin E formulations
containing mixed tocopherols in human subjects."
Raj K. Chopra and Hemmi N. Bhagavan
Internat. J. Vit. Nutr. Res., 69(2), 1999, 92-95

APhA - Poster Presentations

and several others.

Professional Memberships:

- American Pharmaceutical Association
- American Academy of Pharmaceutical Scientists
- Institute of Food Technologists
- National Nutritional Foods Association (corporate membership)